Ellagitannin Chemistry. The First Total Synthesis of a Dimeric Ellagitannin, Coriariin A

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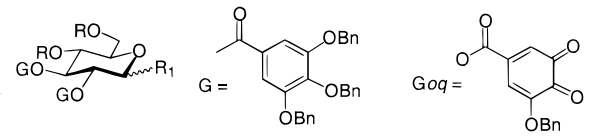
The ellagitannins comprise a vast family of secondary plant metabolites whose likely biogenesis derives from the various combinations and permutations of oxidative coupling between and among their polygalloylated glucose cores.[1] One subfamily of note includes the structurally (but not phylogenetically!) related dimeric ellagitannins agrimoniin, coriariin A (**1**), and gemin A, which are characterized by carbon-coupled glucose-bound galloyl esters (cf. **1**, (*S*)-hexahydroxydiphenoyl, HHDP) and a C−O linkage between the anomeric galloyl units.[2] These species demonstrate very promising tumor remissive properties against several murine xenograft tumor lines.[3] Circumstantial evidence implicates a host-mediated immunostimulatory response rather than direct cytotoxicity in the tumoricidal activity for at least two of these species, agrimoniin[3c,d] and coriariin A,[4] and suggests that further mechanism-of-action studies are warranted. Organic synthesis can contribute to these studies by providing pure and homogeneous ellagitannin[5] as well as structural analogues. In this vein, the development of methodology that enables assembly of members of this class of ellagitannins is described. These studies culminate in the first total synthesis of a dimeric ellagitannin, coriariin A (**1**).

Prior success in implementing a biomimetic strategy for monomeric ellagitannin synthesis suggested that an approach to these more complex dimeric targets might also benefit from consideration of their biosynthesis.[6] Absent any data on this point, speculation that in vivo dimerization of an oxidatively activated tellimagrandin II derivative (cf. **5**) guided the design of the initial synthesis strategy. Dimerization of the simple model system **6** to furnish a dehydrogalloyl ether-containing ellagitannin−gallotannin hybrid gave further support to this plan.[7] Unfortunately, the synthesis and subsequent dimerization chemistry of the related HHDP-containing putative coriariin A precursor **5** proved problematic and eventually this approach was abandoned. The hope that a second-generation approach featuring a three-component coupling with the dehydrodigalloyl ether diacid **4** and 2 equiv of the tellimagrandin trichloroacetimidate **7** was buoyed by the observation that the model trichloroacetimidate **8** coupled smoothly with the tribenzyl ether of gallic acid **13** to furnish the key β-anomeric linkage in the pentagalloylglucose product **9**. However, implementation of this plan again was frustrated by a lack of correspondence between the model compounds and the coriariin A system, as the combination of **8** with **4** did not afford any dimeric ellagitannin product. Consequently, a third-generation approach to this dimeric ellagitannin was devised (Scheme 1). This final strategy utilized galloyl orthoquinone dimerization chemistry, inspired by the presumed biosynthesis, to assemble the dehydrodigalloyl ether diacid **4**[7] but then relied on early attachment of this diaryl ether linker unit to the two glucose cores **3**. In this approach, the more electron releasing and less sterically encumbered O(2) and O(3) TBS ethers of **3** are employed to enhance the prospects for efficient execution of the Schmidt trichloroacetimidate acylation chemistry.[8] Conversion of all of the glucose protecting groups in **2** into the appropriately functionalized galloyl esters then sets the stage for the second key step in this synthesis, the penultimate $Pb(OAc)_4$-mediated double oxidative cyclization of this octagalloylated coriariin A precursor.



5 R = benzylated HHDP, R_1 = β-G*oq*
6 R = G, R_1 = β-G*oq*
7 R = benzylated HHDP, R_1 = α-OC(CCl_3)=NH
8 R = G, R_1 = α-OC(CCl_3)=NH
9 R = G, R_1 = β-3,4,5-(BnO)$C_6H_2CO_2$

The route to coriariin A (**1**) commences with the synthesis of the tetraprotected glucopyranosyl alcohol **3** from the known diol **10**,[6b] Scheme 2. Conversion of this free alcohol to the α-trichloroacetimidate **11** permits testing of the critical bis acylation reaction with known diacid **4**. Simply refluxing 2 equiv of **11** with the diacid **4** in benzene furnishes the requisite diglucopyranosyl dehydrodigalloyl diester **2** in good yield and free of anomeric stereoisomers. The facility of this acylation stands in sharp contrast to the failed attempts with the related O(2),O(3)-digalloylated glucopyranosyl trichloroacetimidate **8**, an observation reminiscent of the results derived from the arming/disarming glucopyranosyl etherification protocols established by Fraser-Reid et al.[9] Electronic influences on trichloroacetimidate acylation chemistry have not been explored systematically, and the results with **8**/**11** suggest that reactivity may be responsive to the electron demand of the O(2) substituent. Much of the remaining synthesis involves orchestration of protecting group removal, as three distinct sets of hydroxyl moieties must be revealed in the appropriate sequence. In particular, the use of TBAF buffered with HOAc was crucial for maintaining the integrity of the sensitive dehydrodigallyl ester bonds during the desilylation of **2**.[10] Other common desilylation protocols (unbuffered TBAF,

(1) See (a) Haslam, E. *Practical Polyphenolics*; Cambridge University Press: Cambridge, 1998. (b) Feldman, K. S.; Sahasrabudhe, K.; Quideau, S.; Hunter, K. L.; Lawlor, M. D. *Plant Polyphenols 2: Chemistry, Biology, Pharmacology, Ecology*; Kluwer Academic/Plenum Publishers: New York, 1999. (c) Okuda, T.; Yoshida, T.; Hatano, T. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1995; Vol. 66, pp 1−117 and references therein.

(2) (a) Miyamoto, K.; Koshiura, R.; Ikeya, Y.; Taguchi, H. *Chem. Pharm. Bull.* **1985**, *33*, 3977. (b) Hatano, T.; Hattori, S.; Okuda, T. *Chem. Pharm. Bull.* **1986**, *34*, 4092. (c) Yoshida, Y.; Memon, M. U.; Shingu, T.; Okuda, T. *J. Chem. Soc., Perkin Trans 1* **1985**, 315.

(3) (a) Miyamoto, K.; Kishi, N.; Koshiura, R. *Jpn. J. Pharmacol.* **1987**, *43*, 187. (b) Miyamoto, K.; Kishi, N.; Koshiura, R.; Yoshida, T.; Hatano, T.; Okuda, T. *Chem. Pharm. Bull.* **1987**, *35*, 814. (c) Miyamoto, K.; Murayama, T.; Nomura, M.; Hatano, T.; Yoshida, T.; Furukawa, T.; Koshiura, R.; Okuda, T. *Anticancer Res.* **1993**, *13*, 37. (d) Murayama, T.; Kishi, N.; Koshiura, R.; Takagi, K.; Furukawa, T.; Miyamoto, K. *Anticancer Res.* **1992**, *12*, 1471. (e) Miyamoto, K.; Nomura, M.; Murayama, T.; Furukawa, T.; Hatano, T.; Yoshida, T.; Koshiura, R.; Okuda, T. *Biol. Pharm. Bull.* **1993**, *16*, 379.

(4) Feldman, K. S.; Sahasrabudhe, K.; Smith, R. S.; Scheuchenzuber, W. J. *Biorg. Med. Chem. Lett.* **1999**, *9*, 985.

(5) Ellagitannins are invariably isolated as complex mixtures from their plant sources. A lack of crystallinity and ready decomposition during isolation and separation can make acquisition of substantial quantities of pure material challenging. See (a) Okuda, T.; Yoshida, T.; Hatano, T. *J. Nat. Prod.* **1989**, *52*, 1. (b) Okuda, T.; Yoshida, T.; Hatano *Heterocycles* **1990**, *30*, 1195. (c) Yoshida, T.; Hatano, T.; Kuwajima, T.; Okuda, T. *Hetrocycles* **1992**, *33*, 463.

(6) (a) Feldman, K. S.; Ensel. S, M. *J. Am. Chem. Soc.* **1994**, *116*, 3357. (b) Feldman, K. S.; Sambandam, A. *J. Org. Chem.* **1995**, *60*, 8171. (c) Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606.

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(8) (a) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141. (b) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731. (c) Schmidt, R. R.; Jung, K.-H. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

(9) Fraser-Reid, B.; Madsen, R. I. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

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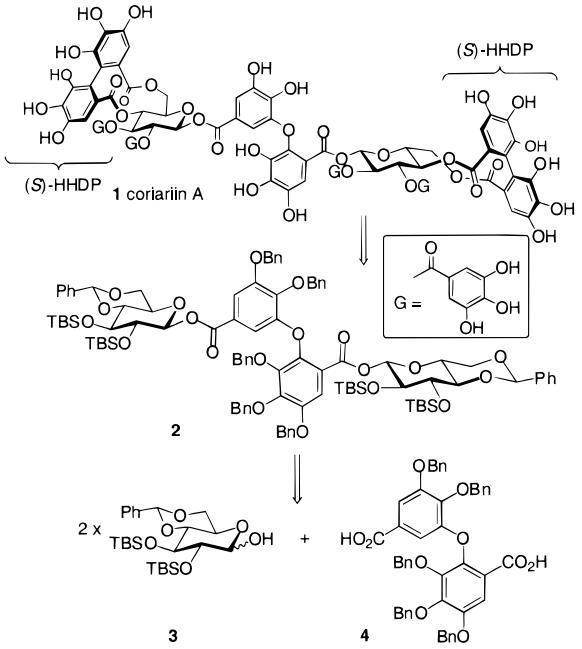
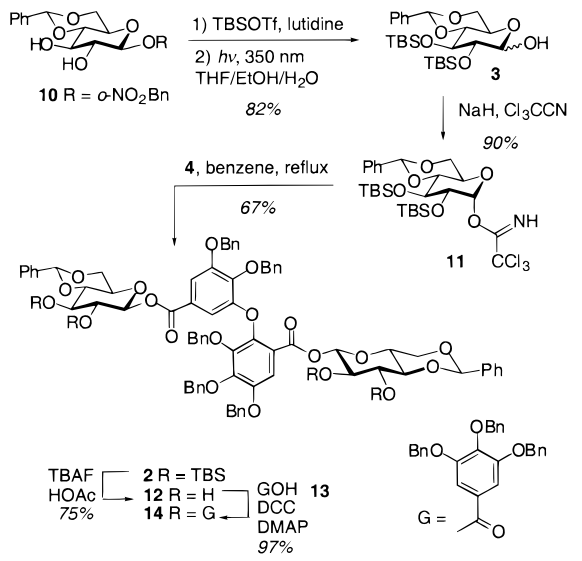
Scheme 1



Scheme 2



TAS-F, HF, HF·pyridine) led to partial or complete anomeric ester hydrolysis. Galloylation of the liberated hydroxyls proceeded efficiently using Keck's modification[11a] of the Steglich esterification protocol[11b] to furnish the hexaester **14**.

Continuation of the synthesis of coriariin A required exchange of the acetal moieties in **14** for protected versions of the Pb(IV)-sensitive galloyl units provided by **16.** Desilylation of the phenolic protecting groups within the octagalloyl dimeric species **17** again required HOAc buffering to preserve the anomeric ester linkages. The derived tetragalloylphenol **18** was subjected to Wessely oxidation,[12] as per the conditions established in earlier digalloyl-to-HHDP transformations,[6] with gratifying results. As anticipated

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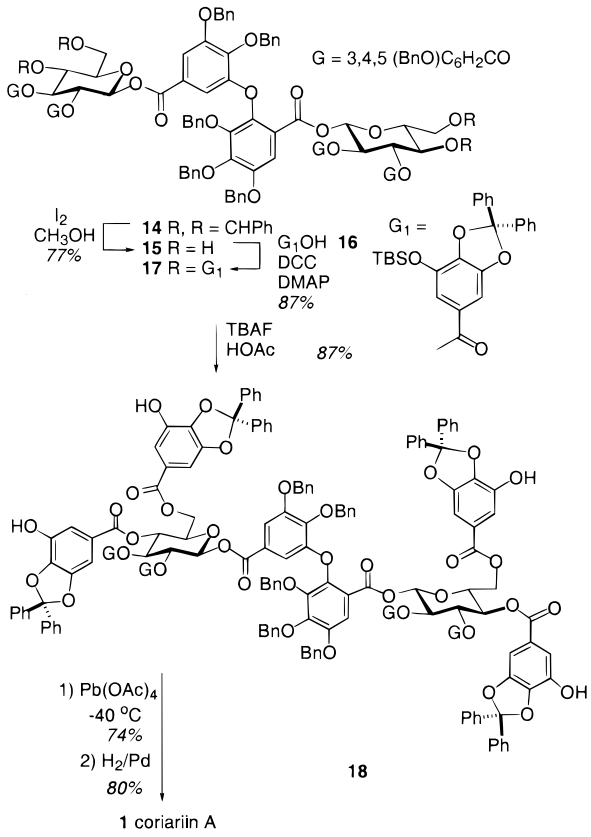
(12) Bubb, W. A.; Sternhell, S. *Tetrahedron Lett.* **1970**, 4499.

Scheme 3



from these earlier studies, the double oxidative cyclization of this tetraphenolic substrate afforded a complex mixture of regioisomeric bis (*S*)-HHDP containing products, a point of no consequence for the coriariin A effort. Hydrogenolysis of all of the benzyl and diphenyl ketal protecting groups furnished coriariin A (**1**) in excellent yield as an off-white solid following trituration with Et_2O and hexane. The equivalence of this synthetic material and the natural product was ascertained by comparison of its ^1H NMR, ^{13}C NMR, CD, and mass spectra with those reported for coriariin A, and by direct comparison of the ^1H NMR spectra of synthetic and natural material (kindly provided by Professor T. Yoshida, Okayama University).

In summary, a stereo- and regioselective synthesis of the naturally occurring dimeric ellagitannin coriariin A (**1**) was accomplished in 11 steps from known diol **10**. Highlights of the synthesis include the bis acylation of an electron-rich glucopyranosyl trichloroacetimidate with a sensitive dehydrodigalloyl diacid, and the double oxidative cyclization of a octagalloyl substrate. This latter transformation establishes the utility of this Wessely oxidation-based methodology in the synthesis of dimeric ellagitannins bearing hydrolytically sensitive dehydrodigalloyl ether linking units.

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Supporting Information Available: Experimental procedures, spectral data (^1H and ^{13}C NMR, IR, LRMS, HRMS, or elemental analysis) for **1**, **2**, **3**, **11**, **12**, **14**, **15**, **17**, and **18**, and copies of the ^1H and ^{13}C NMR spectra for **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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